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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
ZITOMER, S	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)
*U S GPO 2000-473-000/44602

Office Action Summary

Application No.	Applicant(s)
09/715,764	LENZ et al.
Examiner	**Art Unit**
Stephanie Zitomer	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jun 5, 2001 .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-34 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-34 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Informalities

1. The disclosure is objected to because of the following informalities: the word "thymidylate" is misspelled in the claims and throughout the specification.

Appropriate correction is required.

Rejections under 35 U.S.C. 112, first paragraph: Lack of written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are broadly drawn to a method for determining the effectiveness of a large genus of therapeutic regimens which may include administration of a chemotherapeutic drug, i.e., any therapeutic regimen or chemotherapeutic drug, for the treatment of a large genus of cancers in a subject, i.e., any cancer, by determining a large genus of genetic polymorphisms in the subject with the cancer, i.e., any polymorphism, and concluding that the therapeutic regimen will be effective if the genomic polymorphism is "of a certain type". Some of the claims recite a species of one or two genera; none of the claims recites species of all three genera. Compliance with the written description requirement of section 112, first paragraph, requires that claims encompassing genera of elements be supported by description of a representative number of species of elements in each genus. The specification describes a method for determining the effectiveness of a treatment regimen consisting of a single species, 5-fluorouracil (5-FU) (page 12), in subjects with a single species of cancer, colorectal cancer (page 11) by determining a single species of polymorphism, a variation consisting of two or three tandem repeats of a 28 base pair sequence in the 5'UTR of the thymidylate synthase gene (page 6) which variation has been correlated with the subject's response to treatment with 5-FU (page 5). The specification fails to describe a

representative number of species for each genus in the claims because each genus, that is, therapeutic regimen (chemotherapeutic drug), cancer and polymorphism, is extremely large and variable in view of the plethora of known cancers and genetic polymorphisms not to mention those yet to be discovered and the considerable number of extant chemotherapeutic drugs and regimens not to mention those yet to be created such that a single species would not have been considered by the skilled practitioner in the art to be representative of any such large and varied genus. Furthermore, the claimed invention method requires a known correlation between the therapeutic regimen, the cancer and the polymorphism ("concluding that the therapeutic regimen will be effective if the genomic polymorphism exhibited by the subject [with cancer] is of a certain type") and this has been described only for 5-FU, colorectal cancer and TS. As set forth by the Court in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. Clearly, in view of the dearth of representative species for which a correlation of therapy, cancer and polymorphism is described in the specification, the written description does not demonstrate that applicant was in possession of the method as claimed.

3. Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are broadly drawn to a kit "for use in screening for the effectiveness of TS directed drug therapy in human subjects" which encompasses antibodies as in claim 32. However, the specification fails to describe antibodies that would or could be used for such a screen, i.e., no antibodies that detect the genomic polymorphism in the 5'-untranslated region of the TS gene have been identified. Nor are antibodies that might be used in detecting nucleic acid sequences as known in the prior art described in the specification. As to claim 31 which fails to recite any means to be used for the screening, applicant is reminded that limitations in the specification cannot be read into the claims

Rejections under 35 U.S.C. 112, second paragraph: Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The claims are indefinite where the word "effect" and its permutations appear because they are relative terms which are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(b) Claim 1 and claims dependent therefrom are indefinite because the step of "concluding" is *non sequitur* to the step of determining in that there is no recited relationship between the polymorphism and the cancer or between the therapeutic regimen and the polymorphism.

(c) Claims 1 and claims dependent therefrom are indefinite in the recitation "polymorphism of a certain type" because "certain type" is indeterminate and therefore one of skill in the art would not be reasonably apprised of the scope of the claimed invention. Furthermore, "certain type" does not describe the "polymorphism" and thus is not a limitation on the claim.

(d) Claims 2 and others which recite "TS" are indefinite because an abbreviation may have many meanings and it is unclear what is intended by "TS". It is suggested to recite the meaning of "TS" at it first occurrence in the claims with the abbreviation following in parentheses. Thereafter, "TS" may be used in the claims as designating its intended meaning.

(e) Claims 7 and others which recite "UR." are indefinite for the reasons stated above at (b). See the suggested remedy at (b).

(f) Claims 17, 22 and 29 and claims dependent therefrom are indefinite because "associating" is a relational word which requires criteria for determining an "association".

(g) Claim 21 and claims dependent therefrom are indefinite because "most" is a relative term which is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(h) Claim 26 and claims dependent therefrom are indefinite because "poorest", "less poor" and "best" are relative terms which are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(l) Claims 29 and 30 are indefinite because "appropriate" is a relative term which is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of "appropriateness", and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(j) Claim 31 is indefinite because it attempts to define a kit by what it does rather than by what it is. The recited "use" is not limiting on the structure of the kit.

(k) Claim 34 is indefinite because "preferably" renders the claim unclear as to whether the limitations following the phrase are part of the claimed invention. See M.P.E.P. § 2173.05(d).

(l) Claims 17 and 29 and claims dependent therefrom are indefinite in being drawn to a method whereas no method steps are recited. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter the claims encompass as well as make clear the subject matter from which others would be precluded. *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

(m) Claim 17 and claims dependent therefrom lack proper antecedent basis for "associating" because there is no relationship between the "genomic polymorphism" and either gene expression or the therapeutic regimen.

Rejection under 35 U.S.C. 102(b): Anticipation

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Horie et al. (1995) (Cell Struct. Funct. 20:191-197). Horie et al. determined a genomic polymorphism in the form of a 28 bp tandem repeat in the 5' UR. of the TS gene (page 194, Figure 4) which is polymorphic in the number of repeats, two or three, in human subjects and that the level of TS expression is directly proportional to the number of repeats (abstract).

Rejections under 35 U.S.C. 103(a): Obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horikoshi et al. (1992) (Cancer Res. 52:108-116) in view of Horie et al. (1995) (Cell Struct. Funct. 20:191-197). Regarding claims 1-6, Horikoshi et al. disclose a method by which it was concluded that the response of human subjects administered the chemotherapeutic drug, 5FU, which is a TS directed drug, was inversely proportional to the level of TS expression (abstract; page 113, column 2, first full paragraph). The claimed invention method of claims 1-6 differs from that of Horikoshi et al. wherein a genomic polymorphism is determined in the subject with cancer. However, Horie et al. teach that the TS gene has a 28 bp tandem repeat in the 5' UR. (page 194, Figure 4) which is polymorphic in the number of repeats, two or three, in human subjects and that the level of TS expression is directly proportional to the number of repeats (abstract). Therefore, it would have been

obvious to one of ordinary skill in the art at the time the claimed invention was made to determine the subject's level of response to 5FU by determining the level of expression of TS in the subject wherein determining the number of tandem repeats determined the TS expression level and therefore the subject's response to 5FU treatment. It would have been obvious further to determine the subject's TS genotype by analyzing genomic DNA because the skilled practitioner in the art would have been motivated to analyze genomic DNA instead of mRNA as in the references for the known benefit of reducing the time, labor and cost of the analysis.

Regarding claim 7, it would have been understood by one of ordinary skill in the art in view of the reference teachings that the highest expression level of TS and therefore the lowest 5FU response level would be due to a homozygous genotype for three copies of the polymorphic repeat sequence and conversely, the lowest level of TS expression and therefore the highest level of 5FU response would be due to a genotype homozygous for two copies of the repeat sequence. It also would have been understood that an intermediate response level would be due to a genotype heterozygous for the number of repeats, i.e., having one gene copy with two repeats and the other gene copy with three repeats. See Horikoshi et al. at page 113, column 2, first full paragraph, in which some patients had a partial, or intermediate, response to 5FU treatment.

Regarding claim 8, one of ordinary skill in the art would have been motivated to analyze genomic DNA instead of mRNA as in the references for the known benefit of reducing the time, labor and cost of the analysis and to PCR amplify the 5'UTR region containing the tandem repeat as taught by Horikoshi et al. (pages 109-110) in view of routine practice for the known benefit of increasing the amount of nucleic acid available for analysis.

Regarding claim 9, Horikoshi et al. teach analysis of PCR products by electrophoresis (page 110, third full paragraph).

Regarding claims 10-16, it would have been obvious and the skilled practitioner in the art would have been motivated to analyze the TS polymorphism in any cancer treated with 5FU in view of the known variable response to 5FU (Horikoshi et al., page 113, column 2, first full paragraph, and Table 2).

7. Claims 17-21 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horikoshi et al. (1992) (Cancer Res. 52:108-116) in view of Horie et al. (1995) (Cell Struct. Funct. 20:191-197). Regarding claims 17-21 and 26-28, Horikoshi et al. disclose a method by which it was concluded that the response of human subjects administered the chemotherapeutic drug, 5FU, which is a TS directed drug, was inversely proportional to the level of TS expression (abstract; page 113, column 2, first full paragraph). The claimed invention method of claims 17-21 differs from that of Horikoshi et al. wherein a genomic polymorphism is determined in the subject with cancer and the determination is used to predict the effect of a therapeutic regimen. However, Horie et al. teach that the TS gene has a 28 bp tandem repeat in the 5' UR. (page 194, Figure 4) which is polymorphic in the number of repeats, two or three, in human subjects and is involved in the regulation of expression whereby the level of TS expression is directly proportional to the number of repeats (abstract; page 193, last line-page 120, line 11). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to determine the subject's level of response to 5FU by determining the level of expression of TS in the subject wherein determining the number of tandem repeats determined the TS expression level and therefore the subject's response to 5FU treatment. Furthermore, it would have been understood by one of ordinary skill in the art in view of the reference teachings that the highest expression level of TS and therefore the lowest 5FU response level would be due to a homozygous genotype for three copies of the polymorphic repeat sequence and conversely, the lowest level of TS expression and therefore the highest level of 5FU response would be due to a genotype homozygous for two copies of the repeat sequence. It also would have been understood that an intermediate response level would be due to a genotype heterozygous for the number of repeats, i.e., having one gene copy with two repeats and the other gene copy with three repeats. See Horikoshi et al. at page 113, Calum 2, first full paragraph, in which some patients had a partial, or intermediate, response to 5FU treatment. Having determined the subject's TS genotype it would have been obvious to predict the effect and/or determine the effectiveness of treatment with 5FU because the skilled practitioner in the art would have been motivated to spare cancer patients the toxic side effects and wasted time of an effective treatment. Regarding claims

29 and 30, it would have been obvious and the skilled practitioner in the art would have been motivated to use information about the effect of a genomic polymorphism on a patient's response to a chemotherapeutic drug such as that taught in the prior art as detailed above to determine if the drug was appropriate for treating the patient for the obvious benefit of avoiding ineffective treatment.

8. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Horie et al. (1995) (Cell Struct. Funct. 20:191-197) as applied to claims 22-24 above, and further in view of general knowledge in the art. the claimed invention differs from that of Horie et al. in that the reference does not specifically teach a relationship between the number of repeats and the subject's genotype. However, it would have been understood by one of ordinary skill in the art that the highest expression level of TS would be due to a homozygous genotype for three copies of the polymorphic repeat sequence and conversely, the lowest level of TS expression would be due to a genotype homozygous for two copies of the repeat sequence. It also would have been understood that an intermediate expression level would be due to a genotype heterozygous for the number of repeats, i.e., having one gene copy with two repeats and the other gene copy with three repeats in view of general art knowledge regarding alleles.

9. Claims 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horikoshi et al. (1992) (Cancer Res. 52:108-116) in view of Horie et al. (1995) (Cell Struct. Funct. 20:191-197) as applied to claims 1-31 above and further in view of routine practice in the art. The claimed invention differs from the teachings of Horikoshi et al. and Horie et al. wherein reagents for use in screening for the effectiveness of TS directed drug therapy in human subjects are provided in a kit including positive and negative controls, primers, sequencing markers, probes, antibodies and DNA comprising tandemly repeated sequences that determine the TS gene polymorphism type. However, the skilled practitioner in the art would have been motivated to provide the reagents, controls and polymorphic DNA of Horie et al. in a kit in view of routine practice in the art and of the teachings of Horikoshi et al. of the relationship between the TS polymorphism and the effectiveness of chemotherapy.

Prior art of interest

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hughey et al. (1993) (Adv. Exp. Med. Biol. 339:67-76) is cited for teaching that genetic variation in TS is responsible for tumor resistance to 5FU treatment. The patent to Johnston et al. (5,998,151) is cited for disclosing methods for predicting chemotherapeutic efficacy for cancer using antibodies to TS.

Conclusion

11. **No claim is allowed.**

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S. Zitomer

Stephanie Zitomer, Ph.D.

July 2, 2001

STEPHANIE W. ZITOMER
PRIMARY EXAMINER